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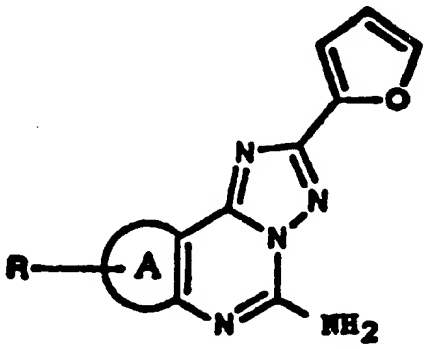
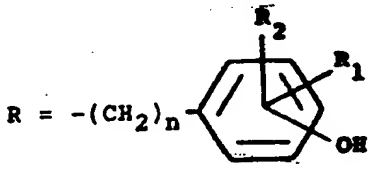
(54) Title: 1,2,4-TRIAZOLO[1,5-c]PYRIMIDINE HETEROCYCLIC ANALOGUES HAVING ANTAGONISTIC ACTIVITY ON ADENOSINE A_{2a} RECEPTOR

(57) Abstract

The compounds of general formula (I), wherein A is a pyrazole, imidazole or triazole ring, R is formula (II), wherein R_1 and R_2, which are the same or different, are H, OH, halogen, C_{1-4} alkoxy, C_{1-4} alkyl, nitro, amino, cyano, C_{1-4} haloalkyl, C_{1-4} haloalkoxy, carboxy, carboxamido groups; moreover the OH group, together with one of R_1 or R_2, or R_1 and R_2, can form the methylenedioxy group -O-CH_2-O-; n is an integer from 0 to 4, are useful as therapeutical agents.



(I)



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1,2,4-TRIAZOLO[1,5-c]PYRIMIDINE HETEROCYCLIC ANALOGUES HAVING ANTAGONISTIC ACTIVITY ON ADENOSINE A_{2a} RECEPTOR

The present invention relates to compounds having antagonistic activity on adenosine A_{2a} receptors.

Adenosine is known to be an endogenous modulator of a number of physiological functions. At the cardiovascular system level, adenosine is a strong vasodilator and a cardiac depressor. On central nervous system, adenosine induces sedative, anxiolytic and antiepileptic effects. On the respiratory system, adenosine induces bronchoconstriction. At the kidney level, it exerts a biphasic action, inducing vasoconstriction at low concentrations and vasodilatation at high doses. Adenosine acts as a lipolysis inhibitor on fat cells and as an antiaggregant on platelets (Stone T.W., Purine receptors and their pharmacological roles. In: Advances in drug research. Academic Press Limited, 1989, 18, 291-429; Progress Cardiovasc. Dis. 1989, 32, 73-97; Williams M., Adenosine and Adenosine receptors. The Humana Press, 1990).

Adenosine action is mediated by the interaction with different membrane specific receptors which belong to the family of receptors coupled with G proteins.

Biochemical and pharmacological studies, together with the recent acquirements in the molecular biology field, have up to now allowed to identify at least 4 different adenosine receptors: A_1, A_{2a}, A_{2b}, ed A_3 (Pharmacol. Rev., 1994, 46, 143-156).

Intense research efforts have made it possible to identify and develop analogs to adenosine able to inte-

ract as agonists with the A_1, A_{2a} and A_3 receptors (Pharmacol. Rev., 1994, 46, 143-156).

The knowledge available on the physiological role of adenosine and its involvement in some pathological processes suggests that selective antagonists for the A_{2a} receptor can be of pharmacological interest. At the level of the central nervous system, antagonistic A_{2a} compounds could have antidepressive properties and stimulate the cognitive functions. Moreover, numerous data show that the A_{2a} receptors are present in high density in the basal ganglia of which the importance in the control of movement is known. Hence, the hypothesis that A_{2a} antagonists can improve motor-impairment due to neurodegenerative processes. Amongst these are included Parkinson's disease, senile dementia as in Alzheimer's disease and psychosis of organic origin (Drug Dev. Res., 1993, 28, 381-385).

At a peripheral level, A_{2a} receptor antagonists could stimulate the respiratory functions and therefore have a therapeutic effect in the treatment of broncho-spasm and, more generally, asthma. Moreover, with regard to the effects at a cardiovascular or renal level, an advantageous activity on renal flow can be envisaged and therefore the possibility of the treatment of renal insufficiency and of various cardiovascular disturbances.

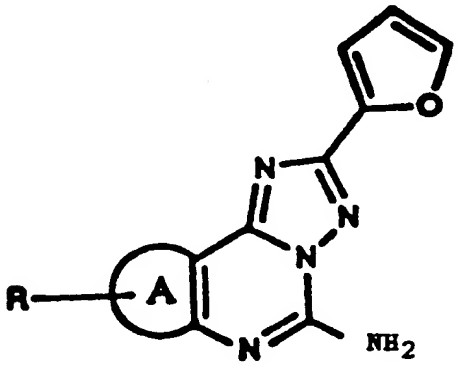
Whilst some xanthine-structure have been known to be A_1 receptor selective antagonists (J Med. Chem., 1992, 35, 407-422), only recently novel xanthine (J. Med. Chem, 1993, 36, 3731-3733) and non-xanthine (PCT WO 9501356, published on 12 01.95, corresponding to Italian

Patent application MI93A001396) Bioorg. Med. Chem. Lett, 1994, 4, 2539-2544) have b en found to have high A_{2a} affinity and moderate A_{2a} vs A_1 selectivity (about 50-fold).

The compounds disclosed in WO 9501356 are 1,2,4-triazolo[1,5-c]pyrimidine heterocyclic analogues, on the heterocyclic ring of which is present, inter alia, an aryl group, particularly phenyl or phenylalkyl, optionally substituted with halogen atoms, C_1-C_4 alkoxy, C_1-C_4 alkyl, nitro, amino, cyano, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, carboxy, carboxamido groups.

Moreover, it has surprisingly been found that the presence of at least one hydroxyl on the phenyl ring gives the compounds disclosed in WO9501356 an increased A_{2a} selectivity.

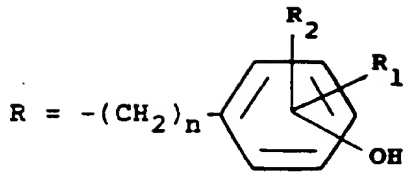
Therefore, the present invention relates to compounds of general formula I:



I

wherein:

A is a pyrazole, imidazole or triazole ring



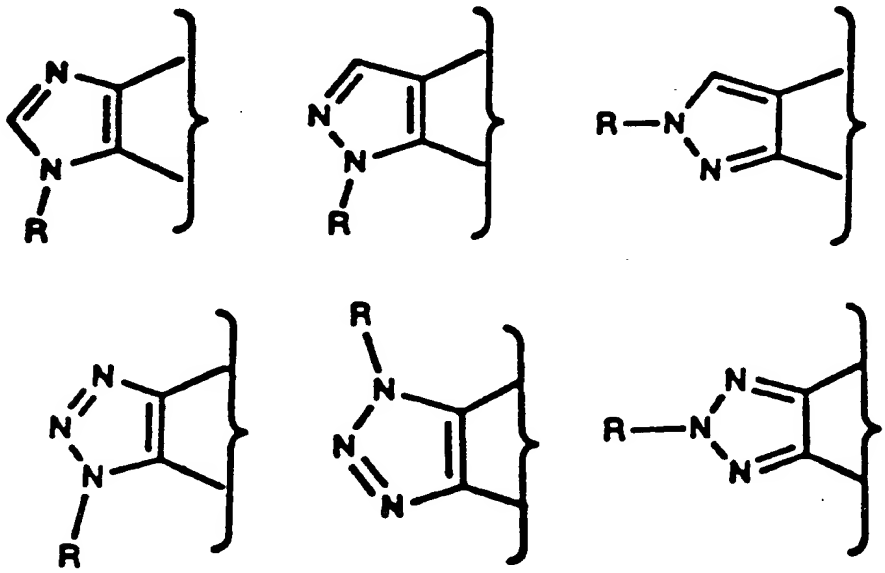
wherein

R_1 and R_2, which are the same or different, are H, OH, halogen, C_1-C_4 alkoxy, C_1-C_4 alkyl, nitro, amino, cyano, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, carboxy, carboxamido groups; moreover the OH group, together with one of R_1 or R_2, or R_1 and R_2, can form the methylenedioxy group -O-CH_2-O-;

n is an integer from 0 to 4.

The invention also comprises the pharmaceutically acceptable salts of the compounds of general formula I.

The possible meanings of A can be represented by the following structural formulae:



Examples of C_1-C_4 alkyl groups include methyl, ethyl, propyl, isopropyl, butyl and isobutyl.

Examples of C_1-C_4 alkoxy groups are methoxy,

ethoxy, propoxy, isopropoxy, butoxy, tert-butoxy.

Halogen atoms are fluorine, chlorine, bromine, iodine.

Examples of C_1-C_4 groups haloalkyl are trifluoromethyl, 2-fluoroethyl, 2-chloroethyl.

Examples of C_1-C_4 haloalkoxy groups are trifluoromethoxy chloromethoxy, 2-fluoroethoxy, 2-chloroethoxy, 2,2,2-trifluoroethoxy.

Preferred compounds of formula I are those wherein A is pyrazolo[4,3-e] or 1,2,3-triazolo[5,4-e].

Particularly preferred compounds of formula I are those wherein A is pyrazolo[4,3-e], n ranges from 1 to 4 included, preferably 2 or 3, the OH group on the phenyl ring is at the para position and R_1 and R_2 are hydrogen.

A second group of particularly preferred compounds of formula I are those wherein A is pyrazolo[4,3-e], n is from 1 to 3, preferably 1 or 2, the OH group on the phenyl ring is at the meta position and R_1 and R_2 are hydrogen.

A third group of particularly preferred compounds of formula I are those wherein A is pyrazolo[4,3-e], n is from 1 to 4, preferably 2 or 3, the OH group on the phenyl ring is at the para position, R_1 is methoxy, preferably at the meta position, R_2 is hydrogen.

A fourth group of particularly preferred compounds of formula I are those wherein A is pyrazolo[4,3-e], n is from 1 to 4, preferably 2 or 3, the OH group on the phenyl ring is at the para position, R_1 is hydroxy, preferably at the meta position, R_2 is hydrogen.

A fifth group of particularly preferred compounds of formula I are those wherein A is 1,2,3-triazolo[5,4-

e], n is from 1 to 4, preferably 2 or 3, and the OH group on the phenyl ring can be at all the possible positions.

Particularly preferred are the following compounds:

5-amino-7-[β-(4-hydroxy-3-methoxy)-phenylethyl]-2-(2-furyl)pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-7-[β-(3-hydroxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-7-[β-(2-hydroxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-7-[γ-(4-hydroxy)-phenylpropyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-7-[4-hydroxybenzyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-7-[β-(3,4-dihydroxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-8-[β-(4-hydroxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-8-[γ-(4-hydroxy)-phenylpropyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-8-[β-(3,4-dihydroxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-8-[β-(3,4-methylenedioxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-8-(4-hydroxybenzyl)-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-7-[β-(4-hydroxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-7-[β-(4-hydroxy-3-iodo)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-7-[γ-(4-hydroxy)-phenylpropyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-7-[γ-(4-hydroxy-3-iodo)-phenylpropyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-7-[β-(3,4-dihydroxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-7-[β-(3,4-methylenedioxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-8-[β-(4-hydroxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-8-[γ-(4-hydroxy)-phenylpropyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-8-[β-(3,4-dihydroxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-8-[β-(3,4-methylenedioxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-7-[β-(4-hydroxy-3-iodo)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-7-[γ-(4-hydroxy-3-iodo)-phenylpropyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-7-[β-(3,4-methylenedioxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

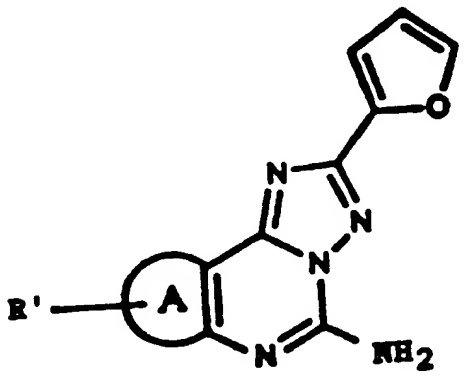
The compounds according to the present invention are prepared with known processes, in particular they are according to the processes described in WO Application 9501356.

As in all the compounds of formula I at least one OH group is present on the phenyl ring, it is necessary

to protect the OH group(s), during the various synthetic steps. The final compounds of formula I are thus obtained by deprotecting the phenyl OH group(s) once the complete structure has been obtained. Protection methods are conventionally known, for example as described in T. W. Greene, P.G.M. Woots, Protective Groups in Organic Synthesis, J. Wiley. N.Y. 1991, 2nd Edition.

A preferred protection method is the benzylation and following debenzylation on Pd/C in tetrahydrofuran. Alternatively, the protection method involves the use of the allyl group or, when two adjacent hydroxy groups are present, the methylendioxy group.

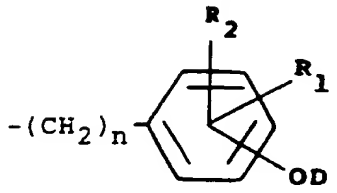
Therefore, another object of the present invention is a process for the preparation of compounds of formula (I), as reported above, which comprises the deprotection of the phenyl hydroxy groups of the compounds of formula (Ia)



(Ia)

wherein:

A is as defined in formula (I);

R'= 

wherein D is a suitable protective group, preferably benzyl or allyl (or $-CH_2-$ as protective group of two adjacent hydroxyl groups), R_1 and R_2, which are the same or different, are hydrogen, OD, wherein D is as defined above, a halogen atom, C_1-C_4 alkyl, nitro, amino, cyano, C_1-C_4 halogen alkoxy, carboxy, carboxamido group; n is as above defined.

The process according to the present invention also comprises the optional transformation of the obtained compound into a pharmaceutically acceptable salt.

BIOLOGICAL ACTIVITY

The pharmacological properties of the disclosed compounds were studied in the most sensitive and suitable experimental models both in vitro and in vivo.

The compounds of general formula I have advantageous properties of selectivity for the A_{2a} receptor compared with those described in the above cited WO 9501356.

Adenosine A_{2a} receptor affinity was tested by means of receptor binding techniques on bovine and rat (Sprague-Dawley strain), cerebellar corpus striatum, which is a tissue rich in A_{2a} receptors. Compound ^3H-CGS 21680 (J. Pharm. Exp. Ther. 1989, 251, 888-893) was used as the radioligand. The A_1 receptor affinity was tested with receptor binding techniques on bovine and rat (Sprague-Dawley strain), cerebellar cortex membranes,

which is a tissue rich in A_1 receptors. ^{3}H-Cyclohexyl-adenosine, ^{3}H-CHA (Proc. Natl. Acad. Sci. - USA - 1980, 77, 5547-5551) was used as the radioligand. The selectivity for the A_{2a} receptor was evaluated from the comparison between the affinities for the A_1 or A_{2a} receptor shown by each compound. A number of experimental data support the evidence that a marked relationship exists between the affinity found with binding techniques in brain tissues and the physiological effects modulated by adenosine receptors.

A_{2a} receptors are mainly present in the vascular system and the stimulation thereof causes vasodilation. Therefore, the A_{2a} antagonistic activity of these molecules has been studied by evaluating the capability of inhibiting vasodilation induced by adenosine agonists in vascular tissues such as rat aorta and bovine or porcine coronary arteries.

These compounds were unable to antagonize negative chronotropic effects induced by A_1 receptor agonists when tested on isolated rat atria (Br. J. Pharmacol., 1983, 78, 207-212).

Another test to evaluate the antagonistic activity of the new compounds is the study of platelet aggregation. In fact, adenosine or the analogues thereof are known to inhibit platelet aggregation induced by different aggregatory agents, among which ADP. Therefore, the capability of the novel compounds of antagonizing the inhibitory effect induced by NECA or CGS 21680 agonists was tested using rabbit platelets.

This test is particularly important as only the A_{2a} receptor is present on platelet cell membranes.

The in vivo activity was evaluated in Swiss mice and spontaneously hypertensive rats (SHR). The behavioural response to a treatment with different doses of the tested compounds administered parenterally was evaluated in the mice. In the SHR rats, the tested compounds were administered parenterally at increasing doses and the capability thereof of antagonizing the bradycardic and hypotensive effects induced by A_1 and A_{2a} receptor agonists, respectively, was measured.

A number of the compounds of formula I showed a marked A_{2a} affinity with Ki ranging from 1 to 10 nM. The A_{2a} selectivity for some compounds is 200-800fold, which is markedly higher than that of the compounds known up to now.

In the platelet aggregation test, said compounds proved to effectively block the antiaggregatory effects induced by A_{2a} agonists, with pA_2 values ranging from 8 to 10.

The compounds of the invention antagonize in a variety of vascular districts, with a similar potency, vasodilatation mediated by A_{2a} receptors, whereas they are not able of blocking the negative chronotropic effect induced by A_1 agonists in rat isolated atria. In the in vivo models, the tested compounds showed a poor stimulating activity on central nervous system, they antagonized the hypotension induced by A_{2a} agonists without changing significantly the heart rate. The compounds turned out to be active at doses from 0.001 to 3 mg/kg intraperitoneally.

For the envisaged therapeutical uses, compounds I will be formulated as suitable pharmaceutical composi-

tions, which can be administered, for example, by the oral, parenteral or transdermal routes, using known techniques and excipients, as described for example in Remington's Pharmaceutical Sciences Handbook, Mack Pub. Co., NY, USA, XVII ed. Said compositions are comprised within the scope of the present invention.

The daily dosage will depend, of course, on many factors (severity of the pathology to treat, patient conditions, toxicology and pharmacokinetic of the selected compound) but generally it will range from 0.01 to 10 mg/kg body weight, preferably from 0.1 to 1 mg/kg, optionally subdivided in more administrations. Examples of pharmaceutical compositions comprise capsules, tablets, solutions, syrups, vials, controlled-release forms, transdermal forms (patches) and the like.

The following examples further illustrate the invention.

Example 1

5-amino-7-[β-(4-hydroxy)-phenylethyl]-2-(furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine.

A solution of 5-amino-7-[β-(4-benzyloxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo-[1,5-c]pyrimidine (1.5 g; 0.003 moles) in THF (20 ml) is added with $HCOONH_4$ (0.81 g, 0.012 moles) and 10% C-Pd (0.3 g) and refluxed for 2 hours. When the reaction is complete, the catalyst is filtered off and the supernatant is concentrated. The residue is chromatographed (AcOEt) to give 0.44 (41%) of the desired compound, which is a white solid, m.p. 265 (dec.). IR (KBr) cm^{-1}: 3500-3100. 1650. 1610. 1525, 1435; ^1H NMR (DMSO) δ: 3.04, (t, 2H, J=8 Hz); 4.41 (t,

2H, J=8 Hz); 6.60 (d, 2H, J=8 Hz); 6.73-6.74 (m, 1H); 6.93 (d, 2H, J=8); 7.22 (d, 1H, J=4 Hz); 7.94 (s, 1H); 8.07 (bs, 2H); 8.16 (s, 1H), 9.22 (s, 1H).

Example 2

0.25 ml of an 1M BCl_3 solution in CH_2Cl_2 were added at 0°C to a solution of 50 mg (0.12 mmol) of 5-amino-7-[β-(3,4-methylenedioxy)phenylethyl]-2-(2-furyl)-pyrazole-[4,3-e]-1,2,4-triazole-[1,5-c]-pyrimidine.

The mixture was left at 4°C for 5 h. 1 ml of methanol was added and the solvent was evaporated, to give 33 mg of the corresponding 3,4-dihydroxy derivative (m.p. 272° dec.).

Example 3

Following the same procedures of Example 1 or 2, starting from the suitable benzyloxy- or methylendioxy-substituted precursors, the following compounds were obtained:

5-amino-7-[β-(4-hydroxy-3-methoxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-7-[β-(3-hydroxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-7-[β-(2-hydroxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-7-[γ-(4-hydroxy)-phenylpropyl]-2-(2-furyl)-pyrazolo[4,3-e]1,2,4-triazolo[1,5-c]pyrimidine;
m.p. 189-191°C;

5-amino-7-[4-hydroxybenzyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine, m.p. > 280°C;

5-amino-8-[β-(4-hydroxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-8-[γ-(4-hydroxy)-phenylpropyl]-2-(2-furyl)-

pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;
5-amino-8-[β-(3,4-dihydroxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;
5-amino-8-[β-(3,4-methylenedioxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;
5-amino-8-(4-hydroxybenzyl)-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;
5-amino-7-[β-(4-hydroxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;
5-amino-7-[β-(4-hydroxy-3-iodo)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;
5-amino-7-[γ-(4-hydroxy)-phenylpropyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;
5-amino-7-[γ-(3,4-dihydroxy)-phenylpropyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;
m.p. 204-206°C;
5-amino-7-[γ-(3,4-methylendioxy)-phenylpropyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine; m.p. 210-211°C;
5-amino-7-[γ-(4-hydroxy-3-iodo)-phenylpropyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]pyrimidine;
5-amino-7-[β-(3,4-dihydroxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;
5-amino-7-[β-(3,4-methylenedioxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;
5-amino-8-[β-(4-hydroxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;
5-amino-8-[γ-(4-hydroxy)-phenylpropyl]-2-(2-furyl)-

1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-8-[β-(3,4-dihydroxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-8-[β-(3,4-methylenedioxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

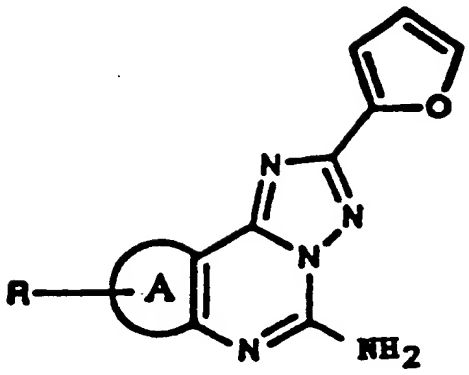
5-amino-7-[β-(4-hydroxy-3-iodo)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-7-[γ-(4-hydroxy-3-iodo)-phenylpropyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-7-[β-(3,4-methylenedioxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine.

CLAIMS

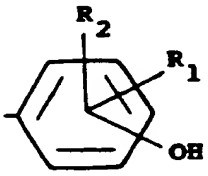
1. Compounds of general formula (I)



I

wherein:

A is a pyrazole, imidazole or triazole ring

R = $-(CH_2)_n$  wherein

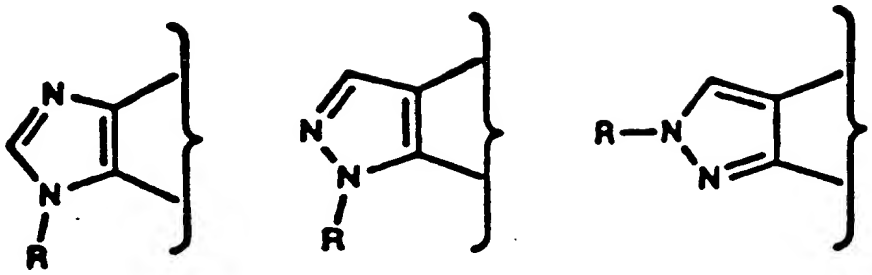
R_1 and R_2, which are the same or different, are H, OH, halogen, C_1-C_4 alkoxy, C_1-C_4 alkyl, nitro, amino, cyano, C_1-C_4 haloalkyl, C_1-C_4 haloalkoxy, carboxy, carboxamido groups; moreover the OH group, together with one of R_1 or R_2, or R_1 and R_2, can form the methylenedioxy group $-O-CH_2-O-$;

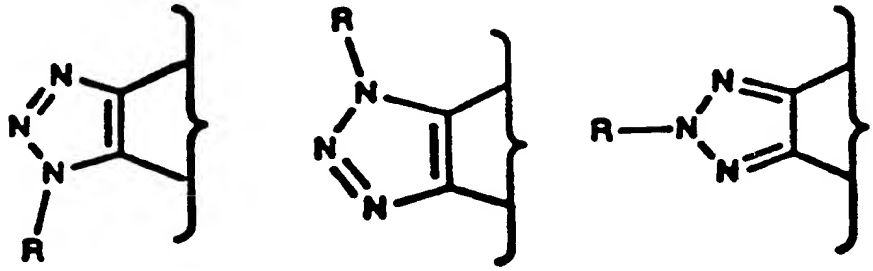
n is an integer from 0 to 4,

and the pharmaceutically acceptable salts thereof.

2. Compounds according to claim 1, wherein A is a

group selected from





3. Compounds according to claim 1, wherein A is pyrazolo[4,3-e], n is from 1 to 4, preferably 2 or 3, the OH group on the phenyl ring is at the para position and R_1 and R_2 are hydrogen.

4. Compounds according to claim 1, wherein A is pyrazolo[4,3-e], n is from 1 to 4, preferably 2 or 3, the OH group on the phenyl ring is at the meta position and R_1 and R_2 are hydrogen.

5. Compounds according to claim 1, wherein A is pyrazolo[4,3-e], n is from 1 to 4, preferably 2 or 3, the OH group on the phenyl ring is at the para position, R_1 is methoxy, preferably at the meta position, R_2 is hydrogen.

6. Compounds according to claim 1, wherein A is pyrazolo[4,3-e], n is from 1 to 4, preferably 2 or 3, the OH group on the phenyl ring is at the para position, R_1 is hydroxy, preferably at the meta position, R_2 is hydrogen.

7. Compounds according to claim 1, wherein A is 1,2,3-triazolo[5,4-e], n is from 1 to 4, preferably 2 or 3, and the OH group on the phenyl ring can be at all the possible positions.

8. A compound according to claim 1, selected from the group consisting of:

5-amino-7-[β-(4-hydroxy-3-methoxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-7-[β-(3-hydroxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-7-[β-(2-hydroxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-7-[γ-(4-hydroxy)-phenylpropyl]-2-(2-furyl)-pyrazolo[4,3-e]1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-7-[4-hydroxybenzyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-8-[β-(4-hydroxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-8-[γ-(4-hydroxy)-phenylpropyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-8-[β-(3,4-dihydroxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-8-[β-(3,4-methylenedioxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-8-(4-hydroxybenzyl)-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-7-[β-(4-hydroxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-7-[β-(4-hydroxy-3-iodo)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-7-[γ-(4-hydroxy)-phenylpropyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-7-[γ-(3,4-dihydroxy)-phenylpropyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-7-[γ-(3,4-methylendioxy)-phenylpropyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-7-[γ-(4-hydroxy-3-iodo)-phenylpropyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]pyrimidine;

5-amino-7-[β-(3,4-dihydroxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-7-[β-(3,4-methylenedioxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-8-[β-(4-hydroxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-8-[γ-(4-hydroxy)-phenylpropyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-8-[β-(3,4-dihydroxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

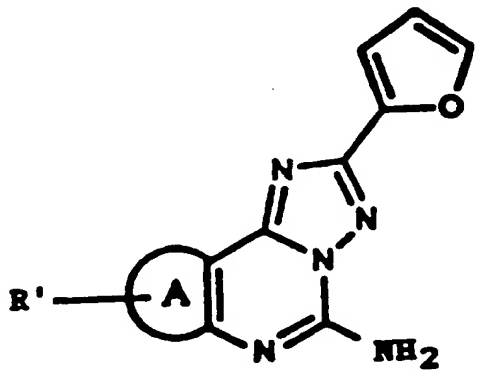
5-amino-8-[β-(3,4-methylenedioxy)-phenylethyl]-2-(2-furyl)-1,2,3-triazolo[5,4-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-7-[β-(4-hydroxy-3-iodo)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-7-[γ-(4-hydroxy-3-iodo)-phenylpropyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine;

5-amino-7-[β-(3,4-methylenedioxy)-phenylethyl]-2-(2-furyl)-pyrazolo[4,3-e]-1,2,4-triazolo[1,5-c]-pyrimidine.

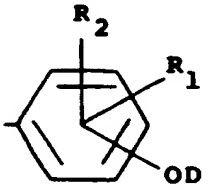
9. A process for the preparation of the compounds of claims 1 to 8, which comprises the deprotection of the phenyl hydroxy groups of the compounds of formula (Ia)



(Ia)

wherein:

A is as defined in formula (I);

R' = 

wherein D is a suitable protective group, preferably benzyl or allyl,

R_1 and R_2, which are the same or different, are hydrogen, OD, wherein D is as defined above, a halogen atom, C_1-C_4 alkyl, nitro, amino, cyano, C_1-C_4 halogen alkoxy, carboxy, carboxamido groups; n is as defined above.

10. A process according to claim 9, wh rein D is benzyl and the deprotection is performed with Pd/C in tetrahydrofuran.

11. A process according to claim 9, wherein the methylenedioxy group is deprotected to dihydroxy derivative.

12. Pharmaceutical compositions containing as the active ingredient a therapeutically effective amount of a compound of the claims 1-8 in admixture with conventional carriers and excipients.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 96/02881

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D487/14 A61K31/495 //(C07D487/14,249:00,249:00,239:00), (C07D487/14,249:00,239:00,231:00),(C07D487/14,249:00,239:00, 235:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO,A,95 01356 (SCHERING PLOUGH S P A ;BARALDI PIER GIOVANNI (IT); ZAPPATERRA LAUR) 12 January 1995 cited in the application see claim 1 -----	1-12

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

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"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
16 October 1996	25.10.96

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	De Jong, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. ...tional Application No
PCT/EP 96/02881

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9501356	12-01-95	AU-A- 7072394	24-01-95